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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/606,222	THOMAS ET AL.	
	Examiner	Art Unit	
	Thai-An N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,20-24,32 and 38-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,20-24,32 and 38-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 2/26/03, Paper No. 15, has been entered. Claims 1, 20 and 32 have been amended. Claims 43-49 have been added.

Claims 1-6, 20-24, 32 and 38-49 are pending and under current examination.

Any rejection made of record in the prior Office action, mailed 11/26/02, Paper No. 14, and not made of record in the instant Office action, has been withdrawn in view of Applicants' arguments and/or amendments to the claims.

Drawings

The corrected or substitute drawings were received on 2/26/03. These drawings are acceptable.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1-6 and 38-42 under 35 U.S.C. 112, first paragraph, is maintained for reasons advanced on pages 2-7 of the prior Office Action.

The specification, while being enabling for a method for deleting a nucleic acid sequence in a specified tissue of a mouse from a DNA molecule introduced into

the mouse, comprising introducing a DNA molecule which comprises a recombinase site, a tissue-specific promoter, a recombinase gene, a foreign DNA and a recombinase site, the specification does not reasonably provide enablement for a method for deleting a nucleic acid sequence in a specified tissue of organisms, to the breadth claimed, from a DNA introduced into the organism, comprising introducing a DNA molecule which comprises a recombinase site, a tissue-specific promoter, a recombinase gene, a foreign DNA and a recombinase site, the growing of organisms, to the breadth claimed, so that the tissue-specific promoter is active for expression of the recombinase gene in the specific tissue, and where the foreign DNA is deleted in the specified tissue during growth of organisms to the breadth claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants submit that the Examiner has misinterpreted the scope of the presently pending claims, or has misapplied applicable U.S. patent law. Applicants argue that the claims, as previously amended, encompass the removal of DNA from an animal cell, after the DNA has been inserted into the cell. Applicants point to the specification which describes a working example wherein DNA is removed from an animal cell after it has been introduced into a cell. Applicants argue that the prior rejections state that certain combinations of the claimed invention are not enabled; and that Applicants do not agree that the Examiner has adequately

provided evidence of any claimed combinations are inoperable. See pp. 6-7 of the Response. Applicants argue that the Examiner has asserted that the claims are not enabled because there is a high degree of unpredictability associated with generating ES cells, generating transgenic animals and effecting germ line gene therapy. Applicants argue that the Examiner ahs improperly cited technical reasons related to the generation of transgenic sequences in animals or cells as evidence of the unpredictability of deletion of such sequences. Further, Applicants argue that without scientific reasons or evidence are not sufficient to sustain an enablement rejection. Applicants argue that regardless of whether the claimed nucleic acid can or cannot be introduced into a given cell or animal, the Examiner has provided no specific technical reasons why the claimed methods will not work in any animal or cell following successful introduction of the claimed nucleic acids into said animal or cell. See p. 8, 1st ¶ of the Response. Applicants further provide abstracts to support that the generation of transgenic organisms is predictable. See p. 1st ¶ of the Response.

Applicants' arguments have been carefully considered, however, they are not found to be persuasive. It is reiterated that the claimed invention encompasses practicing the claimed method in an animal cell, both *in vitro* and *in vivo*. Indeed, further dependent claims recite that the cell is part of a tissue [see claim 39]. As such, the prior rejection is maintained that the claimed invention encompasses on the deletion of nucleic acid sequences from a DNA molecule that has been

introduced into an organism. However, the state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). The art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene (Wall, 1996 Theriogenology, Vol. 45, pp. 57-68). The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, J. Biotech. Vol. 34, pages 269-287, specifically page 281). Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as methylation or deletion from the genome (Kappell, 1992, Current Opinions in Biotechnology, Vol. 3, pp. 548-553).

Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron, 1997, Molec. Biol. 7, pages 253-265, specifically page 256, col. 1 -

2, bridg. parag.). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron, 1997, Molec. Biol. 7, page 256, lines 3-9). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann, 1997, Transg. Res. 7, pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4).

Applicants point to Mullins and Mullins (*Hypertension*, 1993) for support of the predictability for generation of transgenic organisms, in particular the overexpression of hepatic lipase in transgenic rabbits [see p. 9, 1st ¶ of the Response]. It is noted that Mullins states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Further, Mullins (1990, Nature, Vol. 344, 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990, Cell, Vol. 63, 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were

preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats (Mullins, 1989, EMBO J., vol. 8, pages 4065-4072; Taurog, 1988, Jour. Immunol., Vol. 141, pages 4020-4023). Mullins (1996, J. Clin. Invest. Vol. 98, pages S37-S40) disclose that the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another. While, the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic animal, other than the exemplified transgenic mouse, it would have required undue experimentation to predict the results achieved in any one host animal comprising the claimed nucleic acid constructs, the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype.

Applicants argue that the Examiner continues to assert that germ-line gene therapy (integration and expression of a gene into the germline such that it is inherited through multiple generations) is the proposed goal of the application, and Applicants point to the specification to show that, "one useful application of the current invention would be to remove DNA used for gene therapy from the germline

so that it is not heritable." See p. 8, 3rd ¶ of the Response. Applicants further argue that the deletion of DNA using the methods and nucleic acids as claimed could be utilized in cells other than ES cells, and provide the example of egg cells. See p. 8, last ¶ of the Response.

It is maintained that the claimed invention encompasses germ line gene therapy. For example, if two mice whose genome comprises the claimed nucleic acid construct are mated, the resulting progeny would also have a genome which comprises the transgene. In such a circumstance, the transgene would be heritable. Applicants' arguments with regard to ES cells is found persuasive, however, it is noted that an "egg cell" as stated by Applicant could not be used to generate a transgenic organism, as it is unfertilized and has a haploid genome. However, the state of the art of transgenics supports that fertilized eggs (*i.e.,* embryos) could be used to produce transgenic animals. However, for reasons stated *supra*, the resulting phenotype of such animals would not be predictable.

Applicants argue, with regard to the prior Office action's opinion that some of the claims are directed to gene therapy, or use in gene therapy, are not enabled, that the relevant claims have been amended or cancelled to recite molecules or methods for deleting a nucleic acid of interest from a cell, and that the specification clearly shows how to make and use the presently claimed invention, including the presentation of experimental details and results, and Applicants reiterate that it is

not necessary to introduce the DNA constructs into ES cells for the invention to work [see pp. 4-5, bridging ¶].

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving a method for deleting a nucleic acid sequence in the specified tissue of an organism, the unpredictable and undeveloped state of the art for the production of transgenic animals with regard to the resulting phenotype, the lack of guidance and direction provided by the specification to carry out gene therapy as broadly claimed, and the unpredictable and undeveloped art of gene therapy, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-24 and 43-49 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20, as written, is unclear. The claim recites "a foreign DNA" in part (d) of the claim. It is unclear what the term "foreign" means. Foreign to the construct, or to the recipient animal it would be used in, or foreign to both? It would appear that "foreign" is dependent upon the context in which the molecule would be used.

Furthermore, the term foreign DNA encompasses any sequence, expressed or not, even a few base pairs. Claims 21-24 depend from claim 24.

Claim 43, as written, is unclear. The claim recites that that the recombinase gene expressed in "the specified tissue" [see line 6 of the claim], however, the claim is directed to methods for deleting nucleic acid sequences in a mouse cell. Claims 44-48 depend from claim 43.

Claim 47 recites the limitation "the introduction of the DNA molecule into an organism" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. The claim is further unclear because the claim recites that the introduction of the DNA molecule produces a transgenic mouse. It is unclear what organism, other than a mouse, would produce another mouse. Furthermore, the claim is missing method steps. Mere "introduction" of a DNA molecule into an organism would not produce a transgenic mouse, as a transgenic mouse would require that the DNA molecule be stably integrated into the mouse genome to be considered a transgenic mouse. Claim 48 depends from claim 47.

Claim 49, as written, is unclear. For a transgenic mouse to be considered transgenic, the transgene must be stably integrated into its genome. The claim as written encompasses a chimeric mouse.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 20-24, 32, 38-41, 43-45 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. No. 6,537,805 B1 [Melchner *et al.*].

The claims are directed to a nucleic acid molecule comrpsing in sequential order (a) a recombinase site, (b) a regulatable promoter operably linked to (c) a recombinase gene (d) a foreign DNA and (e) a recombinase site. In further embodiments, the recombinase site can be loxP or FRT and the recombinase gene can be Cre or FLP.

Melchner teach a recombinant vector with one transcription cassette containing a sequence containing a promoter linked to a recombinase gene and a second transcription cassette containing a suicide gene which is operably linked to a promoter and the flanking sequences contain recombinase target sequences [see col. 2, lines 19-30]. In particular, they teach that the minimal promoter is one that is regulatable by the presence of a specific transcription factor [col. 3-4, bridging ¶]. The recombinase gene can be Cre or Flp [see col. 3, lines 7-11] and the flanking recombinase sequences can be loxP or Frt [see col. 3, lines 13-18]. Melchner teach

various genes that can be used in the described vector, for example, thymidine kinase. See col. 5, lines 59-67. Melchner teach that selection markers can additionally be inserted into the vectors for selection purposes. Melchner teach that the described vector, when expressed in healthy cells, an intact transcription factor binds to the transcription factor binding site so that the recombinase is expressed, and target sequences within the first and second transcription cassettes is immediately deleted, and as such, the suicide gene is deleted [see col. 4, lines 6-20]. Melchner teach that any promoter can be used with the described vector, such as MMTV, a promoter which is active in mammary epithelial cells. Melchner teach that mouse p53 -/- fibroblasts, derived from p53 knockout mice were infected with the self-deleting retroviral vector and it was found that 100% of all puromycin-resistant clones died because of the missing recombination, whereas in 3T3 cells, 57% survived infection. Melchner teach that this phenotype was based on Cre-mediated recombination which eliminated the majority of the provirus including HSV-TK. See Example 4.

Note that the claims, as written, are anticipated by Melchner because, for example, claim 20 recites a sequential order for the vector, it does not exclude the possibility of other components within that sequential order.

Accordingly, Melchner anticipates the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

TNT

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